PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3266/MNM/lr	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/050246	International filing date *(day/month/year)* 03.03.2004	Priority date *(day/month/year)* 18.03.2003
International Patent Classification (IPC) or national classification and IPC A61K31/704, A61P35/00, A61K31/282		
Applicant PHARMACIA ITALIA S.P.A. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1-4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08.10.2004	15.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ansaldo, M Telephone No. +49 89 2399-7876

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050246

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-14 as originally filed

   Claims, Numbers

   1-18 received on 07.07.2005 with letter of 05.07.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 8-10,12-15

because:

☒ the said international application, or the said claims Nos. 8-10,12-15 with respect tp I.A. relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050246

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7,11,16-18
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Claims 8-10,12-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

The documents cited in the International Search Report (ISR) are numbered in the order of their listing. Unless otherwise specified, reference is made to the passages cited in the search report.

1. Documents D3-D9 all disclose preparations comprising morpholinyl anthracycline derivatives of formulas I-VI for the treatment of tumours.

2. Document D2 in particular discloses a combination of nemorubicin (formula I) with cisplatin for the treatment of hepatocellular carcinoma.

3. The subject-matter of the present application differs from the cited prior art in that morpholinyl anthracycline derivatives are used for the preparation of a medicament to be administered in combination with radiation therapy.

4. The prior art in fact does not explicitly disclose to combine morpholinyl anthracycline derivatives with radiation therapy and does neither report nor suggest that morpholinyl anthracycline derivatives have a radiosensitisation activity.

   Thus documents the subject-matter of claims 1-18 is conisdered to be novel (Art. 33 (1) and (2) PCT) and also involve an inventive step (Art. 33 PCT).

5. For the assessment of the present claims 8-10,12-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the

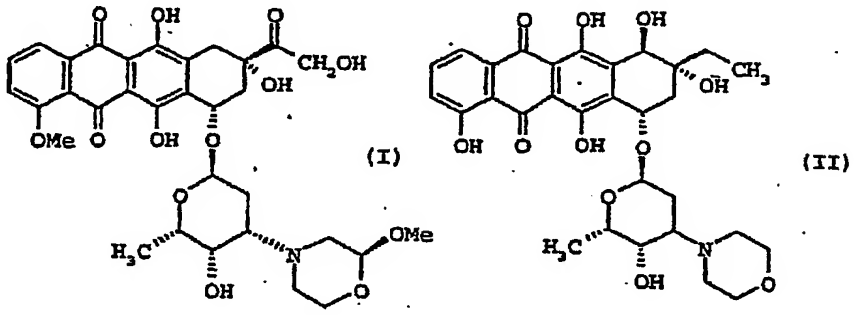
use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

The potential relevant document WO 03 082267 A is quoted according to Rules 70.10 and 64.3 PCT.

Claims

1. Use of ~~A combined preparation comprising~~ a morpholinyl anthracycline derivative having formula (I), formula (II)



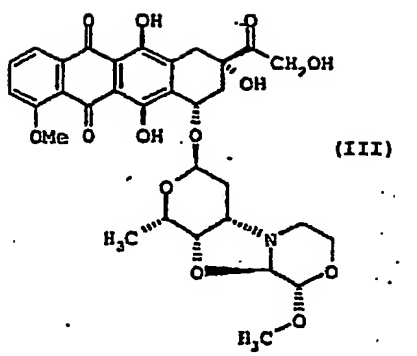
(I) (II)

a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof, ~~administered~~ <-> in combination with radiation therapy.
<in the preparation of a medicament>

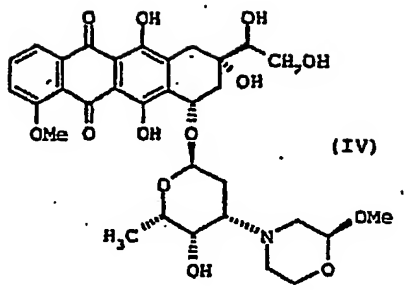
2. The use ~~A combined preparation~~ according to claim 1, wherein the morpholinyl anthracycline is of formula (I).

3. The use ~~A combined preparation~~ according to claim 2, wherein the salt is the hydrochloride salt.

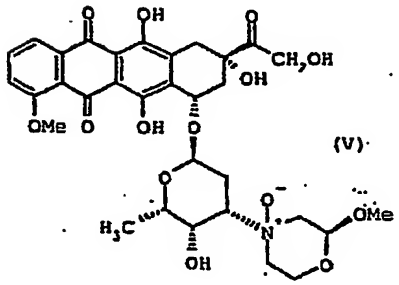
4. The use ~~A combined preparation~~ according to claim 1, wherein the metabolite is a metabolite of the morpholinyl anthracycline derivative of formula (I) selected from the compounds of formulae (III) to (VI)



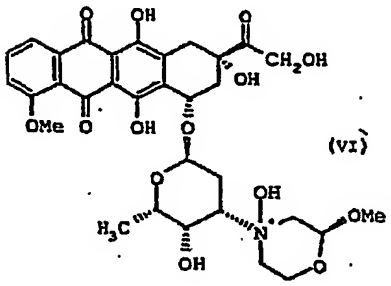
(III)



(IV)



(V)



(VI)

The use of

5. ~~A combined preparation comprising~~ a compound of formula (III), (IV), (V) or (VI) as defined in claim 4, administered in combination with radiation therapy.

The use

6. ~~A combined preparation~~ according to claim 1, for use in the treatment of cancer.

The use

7. ~~A combined preparation~~ according to claim 5, for use in the treatment of cancer.

8. Use of a morpholinyl anthracycline derivative having formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as defined in claim 1, as radiosensitizer.

9. Use according to claim 8, wherein the morpholinyl anthracycline derivative is of formula (I).

10. Use according to claim 9, wherein the salt is the hydrochloride salt.

11. Use of a morpholiny anthracycline derivative of formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as defined in claim 1, in the preparation of a medicament in combination with radiation therapy for simultaneous, separate or sequential use for the treatment of cancer.

12. A method of treating a mammal including a human, suffering from a cancer comprising administering to said mammal a morpholinyl anthracycline of formula (I), formula (II) or a pharmaceutically acceptable salt or pharmaceutically active metabolite thereof as defined in claim 1 and radiation therapy in amounts effective to produce a synergistic anticancer effect.

13. A method according to claim 12, wherein exposure to radiation therapy may either occur simultaneously whilst administering the medicament comprising the morpholinyl anthracycline derivative or, alternatively, sequentially in any order.

14. A method of treating a tumor in a subject in need thereof, comprising sequentially, separately or simultaneously administering

(a) a morpholinyl derivative of formula (I), formula (II) or a pharmaceutically acceptable salt or metabolite thereof as defined in claim 1 to said subject and

(b) radiation therapy to said tumor,

said morpholinyl derivative being administered to said subject in an amount effective to potentiate said radiation therapy.

15. A method according to claim 12, wherein the cancer is a primary or metastatic liver cancer.

16. A combined preparation as claimed in claim 1, which further comprises administering a therapeutically effective amount of a platinum alkylating agent.

17. A combined preparation according to claim 16, wherein the platinum alylating agent is selected from cisplatin, carboplatin, oxaliplatin, nedaplatin and lobaplatin.

18. A combined preparation according to claim 17, wherein the platinum alylating agent is cisplatin.